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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Application of | : | Rowley et al. |
| Application No. | : | 10/069,690 |
| Filing Date | : | August 5, 2002 |
| Art Unit | : | 1616 |
| Title | : | Improved Container Composition for Diagnostic Agents |
| Docket No. | : | PZ9948 US |

Mail Stop Appeal Brief - Patents
Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

## APPEAL BRIEF

Sir:

In response to the Notification of Non-Compliant Appeal Brief (37 CFR 41.37) having the mailing date of September 7, 2005, Appellants submit this amended Appeal Brief in triplicate, appealing from the November 9, 2004 final rejection of the Primary Examiner, in which Claims 1-9 were rejected. The Notice of Appeal was filed on May 4, 2005 and the original Appeal Brief was filed on July 6, 2005. Appellants respectfully submit that the enclosed Appeal Brief is now in complete compliance with 37 CFR 41.37(c).

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Lori Allaire

Signature Lori Allaire

Date Sept 23, 2005

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## I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Amersham plc (now GE Healthcare Limited, a part of General Electric "GE").

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## II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the instant appeal.

## III. STATUS OF CLAIMS

Claims 1-9 are pending in this application. The Examiner has rejected all of these claims. Claims 1-9 as amended during prosecution are reproduced in the **Claims Appendix** attached hereto. Appellants are appealing the rejections of Claims 1-9.

## IV. STATUS OF AMENDMENTS

Appellants filed an Amendment After Final on January 10, 2005, and an advisory action was mailed on January 31, 2005. No claims were amended subsequent to the Examiner's final rejection that was mailed on November 9, 2004.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes a composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, the improvement comprising the diagnostic agent including a non-radioactive metal complex or a hyperpolarized material.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from a Final Rejection that was mailed on November 9, 2004.

The Examiner rejected claims 1-4, and 8 and 9 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,132,409 ("Felder") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). This rejection is respectfully traversed.

The Examiner also rejected claims 1, 5, 6, 8 and 9 under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,545,396 ("Albert") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). This rejection is respectfully traversed.

In addition, the Examiner rejected claims 1, 5 and 7-9 under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 6,466,814 ("Ardenkjaer-Larsen") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). This rejection is respectfully traversed.

Therefore, the issues in this appeal are:

1. Whether Felder in view of Schott Glaswerke or Walther, individually or in combination, disclose or suggest the elements of claims 1-4 and 8 and 9?

2. Whether Felder in view of Schott Glaswerke or Walther contain a motivation to combine one reference with the other reference?

3. Whether Albert in view of Schott Glaswerke or Walther, individually or in combination, disclose or suggest the elements of claims 1, 5, 6, 8, and 9?

4. Whether Albert in view of Schott Glaswerke or Walther contains a motivation to combine one reference with the other reference?

5. Whether Ardenkjaer-Larsen in view of Schott Glaswerke or Walther, individually or in combination, disclose or suggest the elements of claims 1, 5 and 7-9?

6. Whether Ardenkjaer-Larsen in view of Schott Glaswerke or Walther contain a motivation to combine one reference with the other reference?

## VII. ARGUMENT

The Examiner rejected claims 1-4, and 8 and 9 under 35 U.S.C. § 103 (a) as being unpatentable over Felder in view of either one of Schott Glaswerke or Walther.

The Examiner also rejected claims 1, 5, 6, 8 and 9 under 35 U.S.C. § 103 (a) as being unpatentable over Albert in view of either one of Schott Glaswerke or Walther.

In addition, the Examiner rejected claims 1, 5 and 7-9 under 35 U.S.C. § 103 (a) as being unpatentable over Ardenkjaer-Larsen in view of either one of Schott Glaswerke or Walther.

Appellants respectfully request that The Board of Patent Appeals and Interferences ("Board") should reverse the Examiner's rejections for the reasons set forth below.

**A. The Examiner's Rejections of the Claims Should be Reversed Since Felder, Schott Glaswerke, and Walther, Individually or In Combination, Fail to Disclose, Teach or Suggest All the Elements of the Claims**

The present invention is directed to a silica-coated vial containing a specific type of diagnostic agent. "Diagnostic agent" is a term defined in the present application in the first full paragraph of page 4. Moreover, claim 1 further restrictively recites that the diagnostic agent claimed is either a non-radioactive metal complex or a hyperpolarized material.

Felder teaches a plurality of macrocyclic chelating agents and chelates thereof. In several examples, Felder discloses that the solution may be diluted and put into vials. Felder neither discloses the material of the vials nor discusses any specifics of the vials whatsoever.

Schott Glaswerke teaches a silica-coated vial for use with pharmaceuticals or diagnostic agents. Schott Glaswerke provides no further description of the contained material other than this generic reference to 'pharmaceuticals' or 'diagnostic agents'.

Walther discloses a glass tube with an oxide coating. Walther notes that the prior art taught a silica-coated tube for use with (generically) pharmaceuticals. Walther contains no reference to diagnostic agents or contrast agents per se.

The Examiner's rejection is premised on the following:

1. Felder discloses contrast agents in vials.
2. The secondary references provide the significance of contrast agents and other pharmaceuticals in vials.

3. Given the disclosure of Felder of contrast agents and pharmaceuticals in vials, one skilled in the art would be motivated to use improved vials.

Appellants will address each of these characterizations below, but note that the Court of Appeals for the Federal Circuit has outlined the requirements for establishing a prima facie case of obviousness.

First, [i]t is impermissible within the framework of 35 U.S.C. §103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). (emphasis added). Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination. Uniroyal, *Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988). (emphasis added). It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. *Northern Telecom Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (Fed. Cir. 1990). (emphasis added).

Appellants respectfully submit that in the final Office Action dated November 9, 2004, the Examiner has applied Felder not on the basis of Felder as a whole, but by picking out a feature of Felder - the vial - on which Felder does not even elaborate. Appellants point out that the word 'vial' is mentioned briefly in Examples 14-19, but the detailed description at Columns 1-8 plus Examples 1-13 and the claims of Felder are all silent on vials. As stated above, Felder

is directed to macrocyclic chelating agents and Appellants submit that the focus of Felder, as a whole, is on the preparation of chelating agents, not on a 'teaching' that the agents may be put into a vial. Felder provides no description on the details of the vial, indeed there is no suggestion that the vial is critical or even more important to the invention, it is simply what the solution is stored in. No fair reading of Felder provides a motivation that the vial should be improved to the benefit of the invention. Felder seems wholly satisfied with the vial as it is. That the Examiner has fixated on the vial of Felder suggests to Appellants that the Examiner is simply picking and choosing from Felder only that which will support his position, not what Felder fairly suggests to one of ordinary skill in the art.

With respect to the secondary references, Appellants note that the law has long established that "[a] basic mandate inherent in 35 U.S.C. §103 is that "a piecemeal reconstruction of prior art patents in light of the appellants' disclosure" shall not be the basis for a holding of obviousness." *In re Kamm and Young*, 452 F.2d 1052. (C.C.P.A. 1972). Appellants respectfully submit that the Examiner's reasoning regarding these references evidences an improper piecemeal reconstruction of the present invention.

In a final Office Action dated November 9, 2004 ("Office Action") , the Examiner asserts that:

"The secondary references provide the significance of contrast agents and other pharmaceuticals in vials."

Later, in supporting the rejection, the Examiner states that:

"The secondary references teach that pharmaceuticals, including contrast agents, benefit from being in silica-coated vials";

The Examiner then relies on a similar characterization of the prior art at other places within the Office Action.

Appellants question the factual basis for these statements. First, only Schott Glaswerke refers to 'diagnostic agents' while Walther refers only to "pharmaceuticals". These are very broad terms, about as generic as they could possibly be to have any relevance to the present invention. Appellants respectfully submit that the Examiner is committing clear error in paraphrasing these documents as specifically relating to 'contrast agents'. Neither reference uses the term 'contrast agents', let alone the term 'diagnostic agent' as that is restrictively defined and claimed by the present invention, yet the Examiner continuously asserts that these references disclose contrast agents. Appellants respectfully submit that by making such a leap from what the prior art actually states to what the Examiner characterizes the references as stating is an indication of the Examiner's improper use of the Appellants own disclosure as a blueprint for reconstructing the present invention in piecemeal fashion.

Then, in ascribing a motivation provided by the art to combine the references in accordance with the rejection, the Examiner states that all of the teachings in the art would be considered and "given the disclosure of Felder of contrast agents and pharmaceuticals in vials, one skilled in the art would be motivated to use improved vials." Appellants respectfully disagree with such a statement.

The Examiner's assertion is unsupportable because Felder provides no discussion of a vial other than to note one is used to hold the diluted solution. Felder makes no mention of the vial's construction, material or the like. Appellants submit that a more reasonable conclusion is that Felder's utter silence with respect to the vial is that Felder is altogether happy with the vial, identified no problems with it, and hence saw no need to improve it.

Likewise, the Examiner's assertion that given Felder's disclosure of a vial that one would be motivated to use improved vials goes against the Federal Circuit precedent. Indeed the Examiner's reasoning vitiates the Federal Circuit prohibition of 'selective picking and choosing' since it rests on the mere fact that something was disclosed in the reference regardless of the requirement of having to reflect on what the reference as a whole suggests to one of ordinary skill per *Uniroyal*.

Thus, Appellants respectfully submit that by focusing on an extremely minor aspect of Felder, by mischaracterizing the teachings of Schott Glaswerke and Walther, and by failing to properly demonstrate a motivation for combining these particular features of each reference, the Examiner has failed to establish a prima facie case of obviousness against the present invention.

Moreover, the Examiner has rejected Appellants arguments of how Felder teaches away from the present invention. In making his 'teaching away' arguments, Appellants note that the Examiner is incorrect as a matter of law. The Examiner states that "One improvement is not a teaching away from other" [sic]. The Examiner also states that "There is

nothing to suggest that one skilled in the art would limit themselves to the specific benefits taught by Felder". Later, the Examiner states that "a teaching away is provided when the art actually teaching a negative aspect is obtained by a certain modification". Appellants submit that none of these citations are correct – 'teaching away' simply means teaching a solution that would not lead to the claimed subject matter. The Federal Circuit has spoken to this very point:

> **A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant** [emphasis added].
>
> *Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085 (Fed. Cir. 1995).

Therefore, Appellants submit that, contrary to the Examiner's assertions, one improvement can teach away from another, the two improvements may diverge from each other in their teachings. Also, it is incorrect to conclude that "[t]here is nothing to suggest that one skilled in the art would limit themselves to the specific benefits taught by Felder" because such a conclusion requires a negative teaching in order to find a teaching away while it also ignores the requirement to consider what the reference suggests as a whole. Lastly, the *Para-Ordnance* decision clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be found to teach away from an invention.

Thus, by teaching positively towards certain embodiments or features as being important or preferred, the art provides a motivation for the person skilled in the art to go in a particular direction. If that direction leads towards subject matter outside the scope of the claims at issue, then it constitutes a "teaching away". Appellants maintain that the person skilled in the

art, even if assumed to be contemplating improvement of Felder, would focus on the teachings in Felder of embodiments taught to be important, and be motivated to improve those elements. In Felder these are clearly the design of the chelating agent, which is described at length at Column 5 line 25 to Column 7 line 65. That constitutes four columns of text. Again, Felder itself does not even discuss vials or containers, and hence gives no weight to that feature. Felder's emphasis on the chelating agents, and apparent satisfaction with the featureless vial would indicate that improvements to the solution are found by adjusting the formulation of the solution, not by modifying the featureless container.

In the Office Action, the Examiner also dismisses the Appellants suggestion that the Examiner has employed improper hindsight by invoking the language of *In re McLaughlin*. Appellants respectfully submit, however, that the Examiner's rejection takes into account knowledge found in the present application.

The Examiner contends that since silica-coated vials are known to have 'benefits' for pharmaceuticals, one of skill in the art would be motivated to combine such vials with the contrast agents of Felder. If the Examiner is going to treat the present invention as a combination invention, Appellants note that the Federal Circuit has directed for combination inventions that:

> **The initial inquiry should be directed to the vantage point of attacking the problem solved by the invention at the time the invention was made. When prior art itself does not suggest or render 'obvious' the claimed solution to that problem, the art involved does not satisfy the criteria of 35 U.S.C. §103 for precluding patentability.**
>
> *Lindemann Maschinenfabrik GmbH v. AMercan Hoist and Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984).

Appellants have stressed that the present invention describes at length how diagnostic agent metal complexes suffer from unforeseen or variable problems which are solved using silica-coated vials. See page 5 line 1 to page 7 line 22 of the present specification. These problems were not recognized in the prior art, and hence the cited references do not suggest applying silica-coated vials to diagnostic agent metal complexes. The solution to the problem provided by the present claims is therefore believed non-obvious over the cited references.

Further comments on the specific document combinations cited by the Examiner are given below:

**Felder and Schott Glaswerke.**

The Examiner argues that:

"The leaching problem is taught in the art, by DE '958 [Schott Glaswerke], that various pharmaceuticals and diagnostic agents suffer from leaching and that problem can be prevented by using silica coated vials. Clearly, one skilled in the art would see that the benefit would hold true for various pharmaceuticals and diagnostic agents, as taught by DE '958 [Schott Glaswerke], such as the pharmaceutical/diagnostic agents disclosed by Felder."

The Examiner seemingly accepts the fact that Felder itself does not teach or suggest that the diagnostic agent metal complexes described therein suffer from any of the leaching problems. Appellants contend that the Examiner's phrase 'various pharmaceuticals and diagnostic agents' is general only, and fails to demonstrate specific motivation to combine with

Felder. The phrase "such as...disclosed by Felder" confirms that Felder is merely illustrative of *any* diagnostic agent. Such logic merely reiterates the teaching of Schott Glaswerke. It does not show why the specific combination with Felder would definitely have been made.

Schott Glaswerke teaches that glass containers having an inner surface coating of oxides or nitrides of silicon, titanium, tantalum and/or aluminum are useful to reduce leaching of impurities from the glass walls into the contents. There is no teaching or suggestion in Felder that the compositions therein suffer from such leaching problems. Hence, appellants contend that there would be no motivation for the person skilled in the art to modify Felder in the manner suggested by the Examiner.

As noted above, Schott Glaswerke teaches that a very wide range of oxide or nitride coating materials can be used. Hence, the combination of [Felder] + [Schott Glaswerke] leads to a wide range of possibilities, and the person skilled in the art would not be limited to what Schott Glaswerke teaches to be important. Consequently, the combination [Felder] + [Schott Glaswerke] does not distinguish or suggest the specific teaching of the present claims.

Contrary to the Examiner's characterization of Schott Glaswerke as teaching contrast agents (*see above*), DE '958 teaches only blood and blood samples as examples of the "diagnostic solution." Applicants therefore contend that the person skilled in the art would be unlikely to use Schott Glaswerke as a source of teaching applicable to metal complex diagnostic agents which are very different to biological fluids such as blood. Appellants therefore contend that the obviousness objection based on this combination of references is invalid and should be

withdrawn. Reconsideration is respectfully requested.

**Felder and Walther.**

The Examiner asserts that Walther teaches "only three possibilities" and later characterizes this as a 'very limited number of possibilities'. Appellants cannot agree that this is an accurate representation of the teachings of Walther. The Examiner's attention is drawn to Claim 1 of Walther (Column 8 lines 2 to 13), where the phrase "oxide material" is used. Walther uses this same phrase at Column 3 lines 23-39 and Column 4 lines 19-34. Neither the claims nor the specification of Walther limit the "oxide material".

Hence, Appellants contend that Walther in fact teaches that a wide range of oxides are to be used, and that the person skilled in the art would not limit their thinking to what is said to be preferred. Hence, the combination [Felder] + [Walther] leads to a wide range of possibilities, not the specific teachings of the present claims.

Walther does suggest (at Column 4 lines 40 to 43) that $SiO_2$, $Al_2O_3$, $TiO_2$ or mixtures thereof may be used as a preferred embodiment. Even on that teaching, when "mixtures thereof" are permitted, this does not reduce to three possibilities but the following:

$SiO_2$ alone;

$Al_2O_3$ alone;

$TiO_2$ alone;

$SiO_2$ plus $Al_2O_3$;

$SiO_2$ plus $TiO_2$;

$Al_2O_3$ plus $TiO_2$;

$SiO_2$ plus $Al_2O_3$ plus $TiO_2$.

That makes a minimum of seven possible preferred combinations, not three, and for those where there are mixtures there is an infinite range of percentage compositions. Hence, the Examiner's characterization of the teaching of Walther as a choice of three is deeply misleading, and not an accurate reflection of what the reference as a whole suggests or the real choices facing the person skilled in the art upon considering it.

Appellants therefore contend that the obviousness objection based on this combination should be withdrawn. Reconsideration is respectfully requested.

The Examiner's comments with respect to PCVD (Claim 8) are believed moot, since Claim 8 depends on Claim 1, and the above demonstrates that Claim 1 is non-obvious over the prior art of record.

In accordance with the aforementioned, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1-4, 8, and 9 be allowed.

**B. The Examiner's Rejections of the Claims Should be Reversed Since Albert, Schott Glaswerke, and Walther, Individually or In Combination, Fail to Disclose, Teach or Suggest All the Elements of the Claims**

Albert discloses the use of hyperpolarized noble gases for MR imaging. Albert further discloses that the hyperpolarized gas may be stored in a container having a silicone coating [emphasis added].

The Examiner again suggests that it would be obvious to combine the teaching of either DE '958 or Walther on silica-coated vials with the hyperpolarized gas of Albert. The Examiner contends that since silica-coated vials are known to have 'benefits' for pharmaceuticals, one of skill in the art would be motivated to combine such vials with the hyperpolarized gas of Albert. The Examiner's contention seems to be, that if a coating is beneficial to some pharmaceuticals, then it must be beneficial to all pharmaceuticals, without regard to how that coating reacts with the particular pharmaceutical, or in this case, a hyperpolarized gas. These references include using metals within their coatings which are taught herein to adversely affect the polarization levels of a stored hyperpolarized gas. As there is no disclosure, teaching, or suggestion in any of these references to employ only a silica coating so as to not adversely affect the polarization level of a hyperpolarized noble gas, the only motivation for so combining these references is provided by the Appellants' own disclosure.

The Examiner states that "one of ordinary skill in the art would have been motivated to use such silica coated vials for the pharmaceutical compositions disclosed by Albert to take advantage of the one or all of the advantages taught in the prior art in using such vials for pharmaceuticals." Appellants submit that this is another example of the Examiner finding a justification for combining the prior art so as to read on the present invention without regard to what these references, when read as a whole, would fairly suggest to one of ordinary skill in the

art. Albert teaches that silicone should be employed for storing a hyperpolarized gas. One of skill in the art looking at these references would be motivated to follow Albert's specific teachings for preserving the polarization of Albert's own disclosed contrast agent, not the teachings of either Schott or Walther. The Examiner has provided no basis for disposing of Albert's silicone coating in favor of one of the coatings of the secondary references. Once again, the Examiner has used the Appellants' own disclosure as a blueprint for forming an obviousness argument. Since the cited references provide no disclosure, teaching, or suggestion for selecting one of the coatings of the secondary references over the specific coating of the primary reference for use with a hyperpolarized gas, the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Furthermore, the Examiner states in the Office Action that Appellants had previously asserted that "Albert teaches silicon to solve a problem, which is different from silica" and then proceeds to argue against this reasoning. The Examiner then proceeded to question Appellants' references and arguments regarding 'silicon'.

Unfortunately, the Examiner continues to misread Appellants' previous response which clearly referred to Albert's teachings with respect to silicone - which is *very* different from silicon. Appellants reiterate that silicone is indeed a "synthetic polymer containing a repeating silicon oxygen backbone with organic side groups attached *via* carbon-silicon bonds (Merck Index, 13th Edition, entry no. 8569) [emphisis added]. Consequently Appellants arguments were not "somewhat vague" as stated by the Examiner, but factually correct. The Board is invited to study the response as filed in order to confirm Appellants arguments.

Appellants here repeat that Albert, at Example 2 (Column 19 lines 1 to 55, especially lines 8-10), specifically teaches that a silicone coating is to be used and is effective to reduce relaxation of the hyperpolarized $^{129}Xe$ gas on the walls of the glass vessel. The present claims specify silica, ie. $SiO_2$ which is not carbon-containing. Silicon, silica and silicone are very different chemical species, but unfortunately the Examiner seems to be confusing them. These, and the statements made in Albert are matters of fact, which the Board is invited to confirm.

The Examiner incorrectly holds that the Appellants' characterization of Example 2 of Albert is "out of context". Example 2 of Albert refers to silicone coating of glass vessels/containers for the hyperpolarized $^{129}Xe$ gas, and at Column 19 Lines 13-14 to flame sealing. Flame sealing a gas in a glass vessel is standard practice for the storage of gases, and for the Examiner to suggest otherwise is factually incorrect. Thus, Example 2 is entirely consistent with Example 3, and indeed the rest of Albert.

Appellants further refer to the statement at Column 19 lines 8 to 10 of Albert: "The silicone coating apparently reduces relaxation of $^{129}Xe$ on the walls of the glass sphere, permitting creation of larger polarisations."

Thus, Albert provides clear teaching of how to solve the problem of storage of the hyperpolarized gas in glass vessels, by using a silicone coating. The Examiner's combination of

references therefore contradicts Albert itself, and provides no basis for choosing the coatings of Schott or Walther over the coatings of Albert.

In accordance with the aforementioned, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1, 5, 6, 8, and 9 be allowed.

### C. The Examiner's Rejections of the Claims Should be Reversed Since Ardenkjaer-Larsen, Schott Glaswerke, and Walther, Individually or In Combination, Fail to Disclose All the Elements of the Claims

Ardenkjaer-Larsen discloses the use of $^{13}C$-labelled hyperpolarized compounds for imaging.

As has been argued at length above, Schott Glaswerke teaches a wide range of vial coating material possibilities. The combination [Ardenkjaer-Larsen] + [Schott Glaswerke] therefore leads to a wide range of possibilities, which the Examiner has stated the person skilled in the art would consider in full. The combination therefore does not lead to the specific subject matter of the present claims. Consequently, the present claims are believed non-obvious over the combination.

Furthermore, as noted above, Schott Glaswerke teaches only blood and blood products as possible diagnostic agents which could benefit from being used in such coated vials. Hence, the person skilled in the art is unlikely to regard such vials as being useful for very different agents such as $^{13}C$-labelled hyperpolarized materials.

Similar logic applies to Walther, which also teaches a wide range of possibilities, as discussed above. The combination therefore does not lead directly to the specific subject matter of the present claims. Consequently, the present claims are believed non-obvious over the combination.

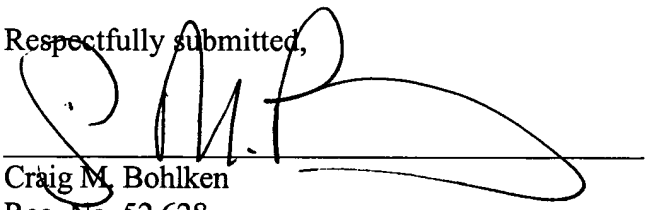
In accordance with the aforementioned, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1-9 be allowed.

## CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 1-9 as set forth in the Office Action mailed November 9, 2004, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: September 23, 2005

Respectfully submitted,



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## XIII. CLAIMS APPENDIX

1. In a composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, the improvement comprising the diagnostic agent including a non-radioactive metal complex or a hyperpolarised material.

2. The composition of claim 1 wherein the diagnostic agent includes a non-radioactive metal complex.

3. The composition of claim 2 wherein the metal complex is an MRI contrast agent.

4. The composition of claim 2 wherein the metal complex is an X-ray contrast agent.

5. The composition of claim 1 wherein the diagnostic agent includes a hyperpolarised material.

6. The composition of claim 5 wherein the hyperpolarised material includes hyperpolarised $^{129}XE$ or $^{3}He$ gas.

7. The composition of claim 5 wherein the hyperpolarised material comprises one or more hyperpolarised $^{13}C$ atoms.

8. The composition of claim 1 wherein the silica coating is deposited by PCVD.

9. The composition of claim 1 wherein the silica coating comprises pure $SiO_2$.

## IX. EVIDENCE APPENDIX

Appellants hereby append copies of the following patents:

U.S. Patent 5,132,409 by Felder;

English translation of German Patent DE29609958 by Schott Glaswerke;

U.S. Patent 6,200,658 by Walther;

U.S. Patent 5,545,396 by Albert; and

U.S. Patent 6,466,814 by Ardenkjaer-Larsen.

This is the evidence relied upon by the Examiner for rejection of appealed Claims 1-9 in the Office Action dated November 9, 2004.

## X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.

Translation of G 1064 and EP 1064

# GLASS CONTAINER, SPECIFICALLY FOR THE STORAGE OF PHARMACEUTICAL OR DIAGNOSTIC SOLUTIONS

## Background of the Invention

Glass containers for the storage of pharmaceutical or diagnostic solutions are intended to come into direct contact with such solutions. Different types of glass containers are used, such as ampuls, small bottles, injection bottles for prefabricated syringes, cylindrical ampuls and container for the taking of blood and blood samples.

It is known with respect to all glass containers—even glass containers made from borosilicate glass which are classified in the highest quality class in accordance with the pharmacopeias (such as the Deutsches Arzneibuch [German Pharmaceutical Book] DAB 10)—that interactions can be documented between the solutions and the glass surface. However, the interactions in the case of glass containers made from lime-natron glass are even substantially greater.

The interaction is based primarily on the leaching of alkalic substances from the glass surface through the aqueous solution. While the solution is being stored, this leaching can lead to an undesired increase in the pH-value (such as in the case of water for injection purposes) of several pH units (see B. Borchert et al., J. of Parenteral Science & Technology, Vol. 43, No. 2 March/April 1989).

With some medications, it is also possible for a portion of the active ingredient to be inactivated by ions dissolved from the glass, which is particularly disruptive in low dosed medications.

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## Summary of the Invention

The task of the invention therefore consists of finding a glass container for the storage of pharmaceutical or diagnostic solutions which behaves in a largely inert manner vis à vis these solutions, i.e., a glass container in which the quantity of ions leached from the glass through the solutions is minimized.

This problem is solved by the glass container, specifically for the storage of pharmaceutical or diagnostic solutions, **characterized by the fact,** that the surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.

## Brief Description of the Drawings

Fig. 1 is a sectional view of the container of the present invention.

## Detailed Description

The inner side of the glass container, i.e., the surface which is in contact with the solutions, is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof; said layer is created by means of a plasma CVD process (PCVD process). Specifically, the layer was manufactured by means of the plasma impulse CVD process (PICVD process).



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In this process, a layer deposition from the gas phase (chemical vapor deposition = CVD) takes place, and the energy necessary for the cleavage of the precursor gases is brought into the system by means of an electric high frequency plasma. This process is well-known, in and of itself.

Surprisingly, it has been shown that a glass container with layers manufactured according to the PCVD or PICVD process possesses a very extraordinary resistance to leaching and thus behaves in a highly inert manner vis à vis the solutions stored therein.

Oxidic layers are particularly well suited, particularly those made from $SiO_2$ and $TiO_2$—with $SiO_2$ being preferred. The thickness of the layers should be about 10 to 1000 ~~µm~~ nm. A thickness of between 20 and 1000 ~~µm~~ nm, particularly 20 to 500 ~~µm~~ nm, is preferred. It is also possible to deposit multiple layers of varying composition to form a layer package; in this connection, it is intended that the layer package has the aforementioned layer thickness.

The composition of the glass from which the container is made is not critical. In general, the usual clear and colored glass for pharmaceutical applications will be used. Preferred, however, is glass which already belongs to a low hydrolytic class, i.e., particularly so-called neutral glass (borosilicate glass) (DAB 10).

By way of example, Figure 1 shows a 10 ml injection glass bottle. The bottle consists of glass 1, whose inner side is provided with a $SiO_2$ coat 2. The thickness of the $SiO_2$ coat is not presented according to scale.

The outstanding properties of the container in accordance with the invention are illustrated by the following example:



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A glass container made from borosilicate glass composed of 75% $SiO_2$, 11% $B_2O_3$, 5% $Al_2O_3$, 7% $Na_2O$, 2% CaO + BaO in the form of an injection bottle with 10 ml capacity, whose inner side has a 150 nm $SiO_2$ layer applied according to the PICVD process, is filled with 2 ml 0.4 mol HCl and then autoclaved for 1 hour at 121° C. Then the quantity of released sodium, calcium, aluminum, borosilicate and silicate cations is determined in µg/l. For comparison purposes, the test was repeated with an identical container which, however, was not provided with an inner coating. The results are summarized in the table.

| | Comparison | |
|---|---|---|
| Cations release | Borosilicate glass without layer µg/l | Borosilicate glass with 150 nm $SiO_2$ layer (µg/l) |
| Sodium (Na) | 3.5 | < detection limit of 0.01 |
| Calcium (Ca) | 1.1 | < detection limit of 0.05 |
| Boron (B) | 3.5 | < detection limit of 0.10 |
| Aluminum (Al) | 2.3 | < detection limit of 0.05 |
| Silicone (Si) | 5.0 | < detection limit of 0.30 |

Each of the indicated values are average values from 32 tested glass containers. In the glass containers according to the invention, the quantity of leached cations always remains below the detection limit. Particularly surprising is the fact that, in spite of an $SiO_2$ concentration of 100% in the layer, the leached quantity of Si ions is distinctly lower than with the comparison sample, despite the fact that, in the latter, the $SiO_2$ concentration in the wall which is in contact with the solution is only 75 percent by weight.



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**What is claimed is:**

1. Glass container, specifically for the storage of pharmaceutical or diagnostic solutions, **characterized by the fact,** that the surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.

2. Glass container according to claim 1, **characterized by the fact,** that the layer is 20 to 1000 nm thick.

3. Glass container according to claim 1, **characterized by the fact,** that the layer consists of $SiO_2$.

4. Glass container according to claim 1, **characterized by the fact,** that the layer is applied by means of a plasma impulse CVD process.



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## ABSTRACT

Glass containers specifically for the storage of pharmaceutical or diagnostic solutions whose surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.




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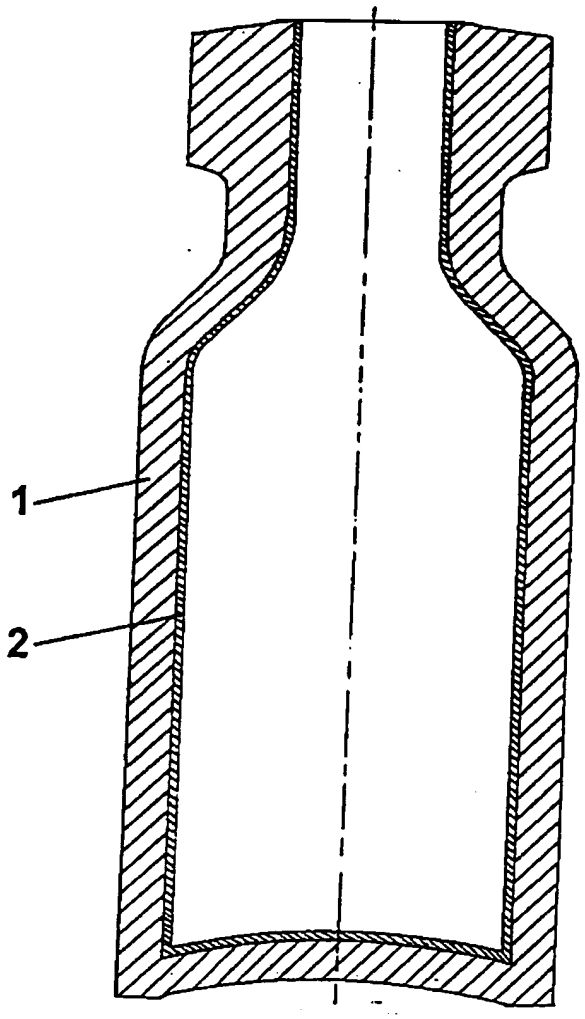



Fig. 1

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